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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/704,159	08/28/1996	JAMES A. WILLIAMS	OPHD-02304	8816
33197	7590	03/09/2004	EXAMINER	
STOUT, UXA, BUYAN & MULLINS LLP 4 VENTURE, SUITE 300 IRVINE, CA 92618			LI, BAO Q	
			ART UNIT	PAPER NUMBER
			1648	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

08/704,159

Applicant(s)

WILLIAMS ET AL.

Examiner

Bao Qun Li

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 113-134 is/are pending in the application.
- 4a) Of the above claim(s) 125-134 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 113-124 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Claims 1-112 canceled. Claims 113-134 are pending. Claims 113-124 are considered before examiner. Claims 125-134 are withdrawn from the consideration.

Response to Amendment

This is a response to the amendment, paper No. 51, filed 10/08/03. Claims 1-112 canceled. Claims 113-134 are pending. Claims 113-124 are considered before examiner. Claims 125-134 are withdrawn from the consideration.

Please note any ground of rejection(s) that has not been repeated is removed. Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
2. Claims 113-114, 116, 119 are still rejected under 35 U.S.C. 112, first paragraph on the same ground as stated in the previous Office Action, because the specification, while being enabling for having a method for producing a soluble recombinant botulinum toxin serotype A by using a vector pHisBot with a promoter T7lac or lacIq T7lac of lacIq T7 in a host cell BL21, does not reasonably provide enablement for having a method for producing a soluble recombinant botulinum toxin with any weak promoter in any host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.
3. Applicant traverse the rejection and submits that an important feature for producing a recombinant botulinum toxin is promoter strength as determined by Dr. Williams. The claims include the feature of "a weak promoter relative to a T7 promoter" for producing the soluble botulinum toxin proteins. As discussed above, is within the skill of a practitioner of ordinary

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skill, a technician, in the field to test promoters that are weak relative to a T7 promoter for soluble botulinum toxin production. Furthermore, applicants argue that the claimed invention is not limited to any particular host cell.

4. Applicant's argument has been fully considered; however, it is not found persuasive because it is unpredictable that the expressed protein is always a soluble one. The solubility of an expressed protein depends on many factors, such as the construct of the protein, the size of the protein, the host cell, the vector used, the promoter used and the condition of fusion protein inducing time and/or temperature etc. For example, LaPenotiere et al. (Toxin 1995, Vol. 33, pp. 1383-1386) expressed recombinant botulinum by using a prokaryotic vector pMAL-p with a lac promoter but in E coil K12 DH5 α host cells, they found that most recombinant fusion proteins were expressed in an insoluble fraction (See last section on page 1386).

5. Applicant's arguments do not comply with 37 CFR 1.111(c) because they do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made. Further, they do not show how the amendments avoid such references or objections.

6. If Applicants wish to claim a method for using a particular promoter to produce a soluble botulinum toxin in a particular host cell BL21, applicants have to amend claims to limit the method by using a particular promoter and host cell because it is unpredictable for claiming any or all promoter weaker than T7 in any or all host cell. Therefore, the rejection is still maintained.

New Ground of Rejection:

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 119 is rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claim 119 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in claim

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113. In that independent claim, applicant has stated that the promoter is a weak promoter relative to a T7 promoter thereby making a soluble botulinum toxin, and this statement indicates that the invention is different from what is defined in the claim 119 because if the promoter as defined by the independent claim 113 as a promoter relative weak than a T7 promoter, promoter as claimed in the dependent claim 119 can not be a T7 promoter, which is contradictory to that of the independent claim 113.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 113-114 and 123 are rejected under 35 U.S.C. 102(b) as being anticipated by Kimura et al. (Applied and Environmental Microbiology 1991, Vol. 57, No. 4, pp. 1168-1172) in light of the disclosure by TaKaRa Shuzo Co. (Catalog of TAKARA BIO INC at the web site: bio.takara.co.jp).

8. Kimura et al. disclose a method for expressing a clostridium botulinum Type C1 toxin by a recombinant phage vector made by inserting the botulinum Type C1 toxin carried by the phage λ gt11 DNA into the pUC118 plasmid vector provided by TaKaRa Shuzo Co after the vector is transfected into a prokaryotic E. Coli MV1184 hot cells, wherein the promoter used for driving the protein expression is a lac promoter, rather than T7 promoter (Please see the Catalog of TaKaRa Shuzo Co. as attached), and the pUC118 is a prokaryotic expression vector. Regarding to the limitation of solubility of the botulinum toxin, Kimura et al. only teach that the recombinant protein of botulinum toxin can be directly detected by using a Western Immunoblot assay in the disrupted cellular supernatant without any procedure of recovering the botulinum toxin from any inclusion body, indicating that the recombinant botulinum toxin expressed by that pUC118 vector is a soluble one (See pages 1168-1169). Therefore, the claimed invention is anticipated by the cited reference.

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Conclusion

No claims are allowed.

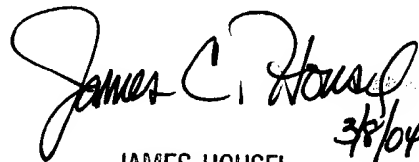
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bao Qun Li whose telephone number is 703-305-1695. The examiner can normally be reached on 7:00 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bao Qun Li

February 23, 2004

Handwritten signature of James C. Housel in black ink, with the date 3/8/04 written below it.

JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600